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HOW A DEVELOPING BRAIN GETS ITSELF PROPERLY WIRED FOR ADAPTIVE FUNCTION*

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Introduction

My title should be qualified with a further explanation that the following consists largely of what might be termed "some scattered views on the old nature/nurture controversy—as seen from a psychobiological standpoint." The questions raised are concerned generally with the extent to which the behavioral properties of the brain are inbuilt, i.e., predetermined by genetic, developmental, and maturational processes, or the other side of the coin, the extent to which the functional plasticity of the brain may be limited by developmental and maturational constraints. If we orient the discussion toward man and the relevant problems of the day, then the primary concern is with the general functional plasticity of human nature, its potentialities and its limitations. To what extent does our genetic endowment, i.e., our hereditary carry-over from the Stone Age, impose important or even limiting conditions on man's capacity to adapt, for example, to the very rapid changes in today's environment and to the even more rapid changes impending.

Functional Interchangeability among Nerve Connections

Thirty years ago when I started working on certain aspects of this general problem with experiments aimed at basic adaptation capacities of the central nervous system, it was the accepted doctrine of the day that the vertebrate brain is possessed of an extreme form of behavioral plasticity with an adaptation capacity almost without limitation. The followers of Pavlov in Russia and of J. B. Watson in this country were

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speculating that it should be feasible with conditioned reflexes and appropriate early training to shape human nature into more desired molds and into a more ideal society. Even the phylogenetically old organization of the spinal cord was thought to be intrinsically plastic and subject to adaptive reeducation. Neurosurgeons the world over were operating during the 1930's on the belief, seemingly supported by dozens of experimental and clinical observations, that they could rearrange the wiring diagram of the nervous system in almost any way desired within the bounds of surgical feasibility, even to the extreme of cross-connecting arm to leg nerves to reinnervate the paralyzed legs following spinal lesions. It was generally agreed that functional readjustment should soon restore proper function to such disarranged structures (Anokhin, 1935; Barron, 1934; Bethe and Fischer, 1931; Pollock and Davis, 1933). Having its wires crossed was no challenge to the brain of the 1920's and 1930's.

In his review of 1939 Kurt Goldstein concluded that it seemed immaterial what particular nerve connections exist; so long as any connections are present, correct function follows. It was about this time also that Karl Lashley was suggesting that if the surgery were feasible, the striate visual cortex could probably be cut free, lifted, rotated, and reconnected 180° out of phase without serious disruption of visual perception. Such was the thinking of the 1930's. (If you hadn't been there, you wouldn't believe it!) On the above terms, where the nerve fiber connections seemed to be functionally plastic and interchangeable, there was no problem in the developmental prewiring of the nervous system to provide for selective growth of proper connections. The general motto of the day was "Let function do it."

When I tried to find out experimentally more about the nature and location of these central reeducative adjustments following surgical transplantation of nerve–muscle and other nerve–endorgan relations, the predicted readjustments simply failed to occur (Sperry, 1940, 1943a,b). After further checks and experiments in rats, amphibians, and monkeys and a critical reexamination of the entire literature I was forced to arrive at a blanket contradiction of the whole plasticity concept as it had previously been applied to nerve–endorgan rearrangements. This whole story was summarized in detail at the time (Sperry, 1945a), and the conclusions still stand so far as I know. The revised interpretation stated that the interchange of nerve connections does in fact cause directly corresponding disturbances of function that are highly intractable to reeducation and in many cases impossible to correct.

The new picture that we emerged with implied a functionally specified system of wired-in behavioral nerve circuits, relatively implastic to rearrangement by function. The whole problem of developmental orga-

nization and the question of how a brain gets itself wired for adaptive function was, of course, markedly changed. We were now confronted with the question of how the proper nerve connections get established correctly in the first place: was this achieved through selective fiber growth or by early irreversible training, or by some combination of the two?

Selectivity in Growth of Nerve Connections

Back in the 1930's it seemed quite inconceivable that highly organized and precisely adjusted behavioral nerve nets could be grown into a brain prefunctionally. The authoritative word on nerve growth stated that the growth and termination of the nerve fibers is nonselective. Electrical and chemical theories for the orientation of growing nerve fibers had seemingly been ruled out during the 1920's and 1930's on the basis of tissue culture observations and a long series of experiments on growth and regeneration of peripheral nerves (Weiss, 1936, 1937, 1938).

When we began experiments to test for selectivity in the growth of central brain tracts, however, like the optic, the trigeminal, the vestibular, tectospinal, and other central nerve tracts, the outcome from the start supported just the opposite conclusion (Sperry, 1945b, 1951a,b). Repeatedly and consistently, the results indicated that nerve growth and connection within the brain and spinal cord proceeds with the utmost precision and selectivity. The most extensive findings were obtained on the visual or retino-tectal system of amphibians and fishes, and this system has come to serve as a simple model for investigation and illustration of many of the basic developmental phenomena now seen to underlie the ontogenetic patterning of brain pathways and fiber connections (Gaze, 1967; Jacobson, 1966; Sperry, 1965a; Sperry and Hibbard, 1968; Szekeley, 1966).

The critical experiments involved an inversion of visual perception produced by surgical rotation of the eye through 180°. This was combined with section and scrambling of the optic fibers that connect the eye to the brain. The objective was to see whether the regrowth of brain connections might restore a confusedly blurred or an orderly type of vision and, if orderly, whether the order would reflect functional adaptation (right-side-up vision) or prefunctional regulation by inherent growth mechanisms (upside-down vision).

The observed result of optic nerve regrowth with eyes rotated 180° was an unambiguous reestablishment of precisely ordered upside-down vision, inverted also from front to back. Behaviorally the inverted vision was highly maladaptive; nevertheless it was found to persist indefinitely

without any significant correction by reeducation. It reverted promptly to normal, however, in an almost machinelike fashion, upon surgical rerotation of the eyeball back to its proper orientation. The result provided a direct answer to the long-standing nativist–empiricist controversy (Walls, 1951) as to whether spatial orientation in visual perception is something that is acquired by experience or something that is innately built into the nervous system.

On a bet that birds would be less rigidly wired than fishes and amphibians, Hess (1956) ingeniously devised a means to outfit newly hatched chicks with spectacles containing prisms that produced an illusory lateral deflection of the visual field 7° to right or left. This produced an initial lateral error of aim in pecking that was measured closely and was observed during the first week of experience to undergo a typical correction curve. The target closed in upon through practice, however, was not the real target but the illusory target displaced to one side. This result effectively put an end to the pages and pages of preceding controversy that had been accumulating in the literature as to whether the early improvement of aim and coordination in this much-studied research model for the nature/nurture issue should be attributed to learning or to maturation.

The new evidence supporting selective growth of nerve connections as the primary basis for functional organization in the visual and other central nervous systems reopened the question of chemical guidance in the growth and termination of nerve fibers. The electrical and mechanical contact guidance theories were clearly inadequate, even in combination, to account for the results. Accordingly, a chemoaffinity interpretation was invoked in which selective affinities at the molecular level were conceived to be operative in intercellular contacts to determine which nerve cells synapse with which. Subsequent experiments extended the concept to the patterning of fiber pathways as well as their terminations (Attardi and Sperry, 1963; Sperry, 1963). Thus the precise ordering of fiber pathways and connections in the prefunctional wiring of brain circuits came to be ascribed very largely to the operation of highly selective cytochemical affinities—an interpretation that still holds.

Scheme for Hereditary Prewiring of Behavioral Nerve Nets

In brief, as we now see it, the complicated nerve fiber circuits of the brain grow, assemble, and organize themselves through the use of intricate chemical codes under genetic control. Early in development the nerve cells, numbering in the billions, acquire individual identification

tags, molecular in nature, by which they can be recognized and distinguished one from another.

As the differentiating neurons and their elongating fibers begin to form functional interconnections to weave the complex communication networks of behavior, the outgrowing fibers become extremely selective about the molecular identity of other cells and fibers with which they will associate. Lasting functional hookups are established only with cells to which the growing fibers find themselves selectively matched by inherent chemical affinities. In many cases the proper molecular match may be restricted further to particular membrane regions of the dendritic tree or soma of the target neuron.

The outgrowing fibers in the developing brain are guided by a kind of probing chemical touch system that leads them along exact pathways in an enormously intricate guidance program that involves millions, in the higher mammals presumably billions, of different, chemically distinct brain cells. By selective molecular preferences expressed through differential adhesivity the respective nerve fibers are guided correctly into their separate channels at each of the numerous forks or decision points which they encounter as they travel through what is essentially a three-dimensional multiple Y-maze of possible channel choices (Sperry, 1963).

Each fiber in the brain pathways has its own preferential affinity for particular prescribed trails in the differentiating surround. Both pushed and pulled along these trails, the probing fiber tip eventually locates and connects with certain other neurons, often far distant, that have the appropriate molecular labels. The potential pathways and terminal connection zones have their own individual biochemical constitution by which each is recognized and distinguished from all others in the same half of the brain and cord. Indications are that right and left halves are chemical mirror maps.

Essentially this amounts to a reinstatement in an extreme form of the old chemotaxis concept of Cajal. It extends the idea of neurospecificity as used earlier in the resonance principle of Weiss (1936) into new dimensions of refinement (Sperry, 1965b), and it extends chemotactic selectivity into areas of organization within the higher centers where the verdict even of Cajal had formerly been "Let function do it."

By tying the chemoaffinity concept of selective nerve growth to a crossed gradient scheme of cellular differentiation and to other basic morphogenetic principles from developmental biology (then called experimental embryology) we were able by the late 1940's to put together what had so long been needed so badly; that is, a fairly credible explanatory picture of the ontogenesis of behavioral nerve nets (Sperry, 1945b,

1951a,b, 1958). In general outline at least, one could now see how it would be entirely possible for behavioral nerve circuits of extreme intricacy and precision to be inherited and organized prefunctionally solely by the mechanisms of embryonic growth and differentiation. In addition to the patterning of fiber pathways and connections, the concept was applied as well to the innate determination of specific physiological properties in different neuronal types and glial elements. Application of this scheme to developmental organization of the human visual system along with other aspects of the general picture were recently reviewed in some detail (Sperry, 1965a).

The foregoing developments in neurogenesis were communicated promptly during the 1940's and early 1950's to the British and European schools of ethology, where they found immediate welcome. The new views in neurogenesis meant that interpretations in ethology where the evidence seemed to favor inheritance of behavior traits no longer need be inhibited by doctrine from the field of nerve growth and development saying, "It cannot be done." The way was now cleared for the much-abused concept of instinct to make its belated if somewhat qualified comeback.

The point of these historical flashbacks is to emphasize the fact that since the year 1940, there have occurred within the biological and closely related sciences, including ethology, profound upsets and polar revisions in our basic thinking relating to the nature/nurture problem. As yet the meaning and impact of these changes has only begun to permeate into areas outside biology and ethology. In the more human areas of behavioral science like clinical psychology, psychiatry, anthropology, education, and the social sciences generally, the prevailing conceptual approach on this subject remains today essentially unchanged or very little changed from where it stood 30 years ago.

Electric Field Theory and Individuality

Another theoretical movement of the 1940's tended to discourage attempts to ascribe inbuilt functional specificity to particular nerve connections. This was the electric field theory of cerebral integration developed in Gestalt psychology which emphasized the regulatory role at cortical levels of holistic pattern and field forces, at the same time deemphasizing the importance of individual neuronal connections (Köhler and Held, 1949). Experiments designed to test for the postulated electric field forces using cortical knife cuts, metallic implants to short-circuit the postulated force fields, and dielectric implants to distort them

(Lashley *et al.*, 1951; Sperry, 1947; Sperry and Miner, 1955; Sperry *et al.*, 1955) yielded results uniformly discouraging to the idea that any major regulative role is played by volume conduction and field effects as postulated in the Gestalt theory. The results favored instead a more traditional fiber circuit form of integration.

The turns taken by the evidence during the 1940's thus brought on all sides a general convergence in neurological thinking toward an ever closer correlation between behavior and brain mechanism, pointing in particular to dependence of brain function upon highly specialized and precisely ordered nerve circuitry patterned around a basic hereditary wiring diagram characteristic of the species. More than this, the hereditary brain structure underlying behavior came to be viewed by Lashley (1947) and others as extending beyond the species level to that of the individual brain. Experts who work intimately with brains in large numbers come to recognize in the surface fissuration of the cerebral cortex, for example, or in cross-sectional features of the thalamus and lower brain stem—whatever one's specialty—almost the same order of individual variation that the average person perceives in faces. Anatomical features of this kind are largely determined at birth. Presumably the inner microscopic and ultrastructural detail of the underlying circuitry is no less subject to individual variation. In general the available evidence along these lines suggests that the individuality we each carry around in the inherent configuration of our cerebral circuitry makes that found in fingerprint patterns grossly crude and simple by comparison.

Corpus Callosum and Organizational Plasticity

As we entered the early 1950's, there remained one further very substantial stronghold for nonconnectionistic theories favoring an extreme functional plasticity in cerebral organization. This was the literature on lesions of the corpus callosum in which complete surgical transection of this largest by far of all the fiber tracts in the brain, containing in man some 200,000,000 fibers, was reported to produce no important behavioral or mental impairments (Akelaitis, 1944). Correlations between brain function and fiber system morphology seemed at the cortical level to be remote to say the least. These observations were being widely used as theoretical ammunition against the role of specific fiber connections in favor of more plastic and in some cases almost mystical concepts of how cerebral organization is achieved. At this stage of our understanding it appeared entirely plausible that whereas fiber connectivity might be critical for orderly function in the sensory and motor pathways and in

the lower centers, the same did not apply to the higher neocortical associations where new and much more plastic forms of integration seemed to prevail.

When we focused a series of experiments on this question beginning about 1952 (Myers and Sperry, 1953), the results failed to confirm the earlier callosum story. Specifically it proved possible with appropriate tests, first in animals and later in human patients, to demonstrate the presence of a large, and still growing, array of distinct functional deficits in interhemispheric integration produced by section of the corpus callosum and the other cerebral commissures (Sperry, 1961, 1968a; Sperry *et al.,* 1969). Instead of opposing connectivity theory, the findings on the corpus callosum have now come to stand as some of the best evidence that we can point to for direct dependence of higher mental functions on specific fiber systems of the cerebral cortex.

Trends toward Nativism

Looking back now in perspective over the developments in psychobiology during the past 30 years, we see a progressive retraction in the claims for functional plasticity and experiential patterning in brain organization. Earlier doctrine on the functional interchangeability of nerve connections, on chemotaxis and the nonselectivity of nerve growth, on empiricist origins of perception, on electric field forces in cortical integration, and on the preservation of normal function after cerebral commissure section has in each case undergone major changes that now point collectively and with mutual reinforcement to a much closer dependence of behavior upon innate brain mechanisms. One may include also major developments within ethology that meantime have moved in the same direction. The gradually increased recognition and acceptance of the role of heredity in shaping behavior has amounted in respect to animal behavior to almost a complete about-face on the old instinct issue. Whereas the very term "instinct" was openly repudiated in professional circles during the 1930's, we find today wide acceptance of the general idea that an entire evolutionary tree can be constructed on the basis of hereditary behavior traits.

The major uncertainties that remain today in the nature/nurture arena are shifted very largely to aspects of human behavior, in which, of course, the environmental and experiential factors attain a sharply increased and paramount influence. Even here, the prevailing shift toward nativism is evident, with the lines between environment and heredity being much more finely drawn than formerly and the questions more

narrowly focused. One need hardly mention that occasional efforts to simply dispense with the whole nature/nurture issue as merely a pseudo-problem have not been exactly helpful from the scientific standpoint.

In recent work with human commissurotomy patients where it is possible to compare the independent performance of the two surgically disconnected hemispheres working at the same task in seriatim, we find new evidence for the intrinsic differentiation of right and left hemispheres in man (Sperry *et al.*, 1969; Bogen, 1969; Sperry and Levy, 1969), and a rationale is seen (Levy, 1969a,b) for the evolution of cerebral dominance and the lateral specialization of function in the human brain. The type of mental processing that one observes when the left hemisphere is in command has been characterized in recent experiments of Levy (1969a) as being verbal, sequential, analytic, logical, and computer-like, whereas that of the right hemisphere contrasts in being nonverbal, spatial, synthetic, insightful, and Gestalt-like. Correlations indicating mutual interference between the right and left forms of mental processing are evident in the test analyses. Thus, a distinct operational advantage can now be seen to having these two rather different and somewhat antagonistic mechanisms for the cerebral processing of information set apart in separate hemispheres.

Further support for this interpretation is found in the analysis of the WAIS subtest scores for left-handers as compared to right-handers (Levy, 1969a,b) and also in the test performance of patients with congenital absence of the corpus callosum (Sperry, 1970a,b). Recent studies of Geschwind (1970) confirm the presence of an anatomical asymmetry in the human brain that correlates with the lateralization of language and cerebral dominance. This anatomical asymmetry, according to Wada (1969), is already demonstrable at birth in stillborn infants—a severe blow to environmentalist theories of the origin of cerebral dominance. In the differential development and balance between the spatially focused faculties of the minor hemisphere, on the one hand, and the verbally focused faculties of the major hemisphere, on the other, one can see a range of possibilities for individual variation in the inherent structure of human intellect.

The infant chimpanzee studies are widely familiar in which attempts have been made to equate environmental factors for chimpanzee and human infants by raising chimpanzees in human households, sometimes along with human children. Attempts at teaching language, toilet training, and general table and house manners to these domiciled chimp youngsters have resulted in showing mainly that chimpanzees are chimpanzees and people are people. Recent work with manual sign language instead of speech (Gardner and Gardner, 1969) looks more promising and certainly offers a more sound approach to the assessment of chim-

panzee intellect. At this date the results remain somewhat ambiguous, and may yet go down in the record as a monument to what a tremendous investment in time, money, and manpower is required to get into the chimpanzee brain a modest number of trained movements and cerebral associations that reflect an order of mental complexity relatively little above what might be expected from a trained dog. Much the same can already be said apparently for the efforts during the past decade to develop communication between people and porpoises.

Among the more relevant studies that deal with the development of intellect in human infants, one perceives today another important and growing trend toward nativism, based to a large extent on emerging evidence that infants and children undergo an orderly, preprogrammed sequence of maturational steps through different levels and kinds of mental achievement. It is commonly stated in human psychology that the first 4 to 6 years of life are the most important in determining the type of person an individual is to become. The implication generally has been that subtle events in the way the child is mothered, nursed, weaned, toilet trained, exposed to different experiences, and what-not make all the difference in shaping the end product during these tender, critical years. From the biopsychological standpoint one strongly suspects that the reason these first years appear to be so influential is not because of the experiential happenings primarily but because of the preprogrammed maturational processes that unfold with great rapidity during these first years. It is during these years that the particular array of genetic factors that shape the basic behavioral tendencies of each personality begin to unfold and gain behavioral expression.

The potency of learning and memory, by contrast, are at their minimum level during this same period. One wonders if it is not more in the deep recesses of questionable psychiatric theory than in the minds of infants that the Oedipus and other such complexes really thrive. Infants and very young children would seem by nature to be comparatively resistant to psychic damage. Much more than in later years, the tendency in ages 1 to 4 is to accept and forget. This applies to ordinary, average growth and experience, not to extremes of experiential deprivation and trauma. Nor does it at all follow from any of the foregoing that learning and experience are therefore unimportant. We assume throughout that all are in common agreement on a starting ground rule which recognizes that both learning and innate factors are critically involved, especially at the human level, and that we are therefore talking always about a balance of emphasis. We assume also that any statements must be appraised in the frame of reference of the questions being asked. Accordingly, it may be inferred from the preceding discussion that the role of

heredity in the regulation of behavior has been generally underestimated during the past 50 years, and the role of experience has been correspondingly overrated.

Avid environmentalists may still prefer to believe that the morons, the Beethovens, the idiot savants, and the Leonardos, the mongoloids and the Einsteins, the Bachs, imbeciles, and Shakespeares, etc. among us (and the in between et ceteras) are distinctive primarily because of the environment and training. If so, they would do well to study the growing literature of behavioral genetics to which no more than this brief reference is included here. It now seems more difficult to find a human trait that is not significantly influenced by heredity than one that is (Fuller and Thompson, 1960; McClearn and Meredith, 1966). The kinds of behavioral traits that to date have been reported to show in man significant hereditary variation extend into quite complex, profound, and subtle personality and intellectual features involving the highest as well as the lowest levels of that complex we call human nature.

Geneticists take for granted that hereditary differences tend to increase as one goes from identical twins to siblings to near relatives to distant relatives to nonrelatives to species, genera, etc. We note that many of the hereditary behavioral differences reported for man have been demonstrated among offspring of the same parents where one would least expect the hereditary effects to be prominent. Some of the best studies involve comparisons between monozygotic twins and dizygotic twins based on the assumption that the monozygotic twins should be identical in innate constitution. There are slight complications in this assumption, one of which stems from the lateral dominance considerations referred to above. Identical twins tend to be one right-handed, the other left-handed, for developmental reasons. They are reported to show a reversed laterality in alpha activity (Fuller and Thompson, 1960), and in the extreme this mirror-image tendency may extend into hair whorls and even situs inversus of the heart. Where the twins happen to be genetically heterozygous with respect to handedness and cerebral dominance, the left-handed tendency is more labile and may be overcome by training pressures in this right-handed world. It has been mentioned above that the tendency toward cerebral ambivalence found statistically among left-handers appears to handicap somewhat against minor hemisphere functions, statistically speaking. These complications in laterality and cerebral dominance that tend to make identical twins not so identical in their innate cerebral constitution, if taken into account in the twin studies, should have the effect of making the hereditary influence appear stronger than it already does.

Plasticity of Neural Maturation

Pertinent evidence regarding the behavioral potency of cerebral plasticity has come from the kind of compensation achieved after early brain damage or after agenesis of specific brain structures like the cerebellum or corpus callosum. Compared to the fully developed brain, the still-growing or maturing brain exhibits significantly greater compensatory capacity. Special interest stems from the promise these anatomical situations hold for a direct approach to the structural and physiological basis of the observed plasticity.

We have been fortunate recently in having available for study an exceptionally asymptomatic case of callosal agenesis, a young woman with total congenital absence of the corpus callosum. We were able to make direct comparisons of her performance with that of patients in whom surgical disconnection of the hemispheres had been carried out in the adult (Saul and Sperry, 1968; Sperry, 1968b). This agenesis patient was a 19-year-old college girl who had maintained a scholastic average of about C or slightly above and who had always been presumed by herself and family to have been entirely normal until X-rays taken after a bout of headaches revealed a total absence of the corpus callosum. She recovered promptly with treatment, and during the following year she cooperated in taking the entire series of tests that we had previously worked out for demonstrating the symptoms of hemisphere disconnection in adult surgical patients.

The majority of the test tasks on which the surgical patients did poorly or failed completely, this agenesis patient passed without any apparent difficulty, performing essentially like a normal control. In particular the direct disruptions between basic right–left cross integrations that persist for years after operation in the surgical patients appeared to have been rather fully compensated. For example, she could readily and promptly read words flashed into either half field of vision or words extending across the midline, half in the left and half in the right visual fields, even when these were presented near the threshold for visual acuity. She also could respond promptly with the sum or product of two numbers flashed simultaneously, one in the left and one in the right visual field. These and related aspects of this case are reviewed elsewhere (Sperry, 1968b).

Further tests were then applied involving more complex and generalized tasks that call upon cooperation between the mental specialties of right and left hemispheres. The baseline for comparison here was obtained from normals rather than from the commissurotomy patients.

These later results indicate that compensation for absence of the corpus callosum is far from complete, leaving a definite handicap in the form of a mild minor hemisphere syndrome (Sperry, 1970a,b). Accordingly, we now distinguish between functions of the callosum that can, and those that cannot, be compensated for in agenesis. With regard to those that *are* compensated, we get some insight into the kind of basic plasticity of which the human brain is capable at best. I say, "at best," here because the defect is present from the early beginning, catching developmental, maturational, and functional forms of compensation from the start, and also because it is part of the neocortical system that is involved, presumably the most plastic in the brain.

At the behavioral level the compensatory achievements, like that for integration between right and left visual hemifields, appear remarkable indeed and are not easily explained with information at hand. The underlying factors that we consider most probably responsible include the following: (a) bilateral development of speech; (b) slight enlargement and reinforced use of the anterior commissure; and (c) slight enlargement and enhanced use of the ipsilateral sensory, motor, and associated interneuron systems of the brain. The ipsilateral components normally are weak but known to be substantially potentiated after birth injuries. The kind of neural compensation here envisaged thus consists mainly of the enhanced use of neural systems already present and provided for in development rather than the creation of entirely new neural systems under functional demand. Recent reports of increased collateral sprouting and even growth of novel connection patterns in the mammalian optic system after early brain damage (Goodman and Horel, 1966; Schneider and Nauta, 1969) look suggestive. It is easy to think of a persisting pressure for diffuse growth of new connections among late maturing microneurons that become ordered secondarily through functional reinforcement and/or disuse atrophy. One must remember, however, that it has yet to be demonstrated that the changes in circuit morphology effected by experience consist of more than an enhancement, maintenance, or neglect of connections that already are basically patterned by selective growth.

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Discussion

R. Oppenheim: In the course of the discussion, Dr. Sperry stated that the remarkable differences often observed between early and late (i.e., young and adult) central nervous system lesions can be explained by the undamaged structure on the contralateral side of the nervous system assuming the function of its damaged counterpart. However, in many of these cases bilateral damage has been done. For example, in the Kennard study, the motor and premotor areas in both hemispheres were destroyed in young monkeys. They exhibited a profound recovery of motor function when compared to the effects of comparable damage to adults.

Results such as these, in my opinion, necessitate the postulation of a different kind of developmental mechanism than the highly specific one that Dr. Sperry has so elegantly worked out in the visual system and in the other long-fiber systems. The possibility of greater plasticity in the making or remaking of synaptic connections in both these longer fiber systems and especially in the shorter ones associated with interneurons or microneurons would seem to be called for on the basis of behavioral evidence such as the Kennard study.

I think there already exists in the literature models of possible mechanisms for the mediation of such plasticity in neuronal maturation. One such example is the phenomenon of collateral sprouting where partial denervation appears to trigger the growth of nerve sprouts from intact fibers in the denervated region. These sprouts then reinnervate the nerveless structure. This phenomenon has already been identified in peripheral motor, sensory, and autonomic systems after denervation and in normal neuromuscular systems.

Another example that is somewhat more speculative at present concerns the well-worked-out phenomenon of amphibian limb regeneration. Mature differentiated cells (muscle, bone, blood vessels, etc.) are somehow triggered by amputation to revert to a more embryonic undifferentiated state. They then redifferentiate into mature cells to form a new limb. At present it is not known to what extent the dedifferentiated cells regain their embryonic pluripotency. But, assuming that they do, and assuming that certain cell types in the central nervous system retain this capacity, such phenomena as recovery of function, differences between early and late lesions, etc., could be better understood. It would only be necessary that cells can make new and different kinds of synaptic connections upon injury to an adjacent part, not that they must undergo complete redifferentiation. However, the last possibility should not be ruled out at this time.

One other possible mechanism for explaining plasticity, especially regarding the so-called early experience effects, has been recently clarified by the work of Altman. He has shown that in certain cell types in the brain of various mammals nerve cell proliferation—and the subsequent stages of migration, growth, and differentiation—

continues well after birth. These findings at least raise the possibility that early experience, stimulation, etc., in one or more of these developmental stages could somehow modify or influence nerve cells, including the kinds of synaptic connections these cells make or accept upon their soma or processes.

There are other possible systems or mechanisms for explaining neural maturation and the making of synaptic connections than the one that Dr. Sperry has identified. Neither type of mechanism precludes the other. They both seem necessary to explain all the behavioral information available.

Dr. Sperry: Learning and the functional plasticity of neural maturation have certainly to be explained at the level you discuss. I think we agree on some of these points.

S. M. Crain: Jacobson (1969) recently published similar views to those suggested by Dr. Oppenheim, and he postulated that plasticity may be particularly characteristic of certain types of small interneurons that differentiate relatively late during central nervous system development. Now, couldn't the dichotomy that we've been discussing be related to a basic difference in the types of neurons that compose the central nervous system? The larger neurons, with long axons, appear to be clearly involved in point-to-point specificity relationships, as Dr. Sperry has so elegantly described. However, small interneurons, with short processes, many of which are still undergoing cell division late in development, may not begin to differentiate until a major portion of the central nervous system is already functioning, in the postnatal period. Perhaps these neurons are much more plastic than neurons which differentiate at an earlier stage, when relatively little function is occurring in neighboring neurons. Selective interference with the differentiation of these late developing neurons may lead to decreased plasticity in this modified central nervous system. It may be possible, for example, to utilize a mitotic inhibitor, e.g., colchicine, at critical stages in central nervous system development, just as this agent has been used by Beidler (1965) to selectively destroy taste cells—which continue to divide frequently even in the adult organism. Just as taste functions can be selectively blocked by systemic introduction of colchicine, we may find that immature animals injected with this drug, at a critical stage when these small interneurons are dividing at a maximal rate, may show less plasticity than normal, especially in higher mammals. I wonder if Dr. Sperry has any comments regarding such a neurocytologic basis to the wide variability in plasticity properties associated with different parts of the central nervous system.

Dr. Sperry: It is true that our direct evidence regarding the developmental patterning of neural connections comes primarily from observations on long-axon systems composed of Cajal's type I neurons. It is also an old speculation that continues to seem reasonable (Sperry and Hibbard, 1968) that the plastic changes imposed by function are located not in these long-axon systems but in Cajal's type II neurons. These latter are still maturing in man apparently at 12 years of age and later. Chemical, including drug, and nutritional, treatments to enhance the potentialities of the small interneuron system certainly hold exciting possibilities. None of this would alter the general point made above concerning our widespread underestimation in recent decades of the importance of genetic determinants.

T. E. McGill: My remarks concern only a minor point in Professor Sperry's presentation, but I should like to question the assumption that laterality is genetically determined. R. L. Collins (1968) has recently performed some very interesting experiments on paw preference in different inbred strains of mice and F_1 crosses between inbred strains. Collins measured paw preference by allowing hungry animals access to a small test tube into which they could reach for bits of food.

In interpreting Collins' results it is important to keep in mind that all members of a given inbred strain are, theoretically at least, genetically identical except for sex differences. This is also true for F_1 animals from a cross between two inbred strains.

Now, under the assumption of genetic determination of laterality, Collins' experiment has several possible outcomes. First, mice might not have a preferred paw, in which case the distribution for any genotype should show a modal value of about 50%. Second, all mice, regardless of genotype, might have the same lateral preference. And, third, some strains might be "right-pawed" and others "left-pawed." Considering the large number of behavioral characteristics for which strain differences have been reported, the latter result might be predicted.

None of these results occurred in Collins' experiment. Rather, for every genotype he studied, a distinct bimodal distribution of paw preference was found. Furthermore, the distributions tended to be symmetrical, with half the mice preferring the right paw and the other half preferring to use the left. The preferences were consistent over time and were correlated with "grip strength" within subjects.

Collins has also reanalyzed published data on the inheritance of laterality in humans and found no evidence for genetic determination of the trait.

Paw preference in mice and handedness in humans, then, may be determined by nongenetic factors, or at least by nonchromosomal factors.

Recent work by Williams (1969) using inbred strains of rats and monozygous quadruplet armadillos has shown very large intrastrain differences in many morphological and biochemical characters. Williams has speculated that these differences may be due to nonchromosomal, probably cytoplasmic, factors. It is possible that such characters as cerebral dominance and laterality are so determined.

Dr. Sperry: Is the tendency for one monozygotic twin to be left-handed, the other right-handed, inherited or not? The "steps-removed" between gene and adult character are often many and varied and the exact nature of the developmental mechanisms involved, while interesting of course to the developmental biologist, may or may not be critically relevant from the behavioral standpoint.

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